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TITLE OF THE INVENTION (280 characters max)

SELECTIVE ESTROGEN RECEPTOR MODULATORS

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25885

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ENCLOSED APPLICATION PARTS (check all that apply)

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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

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Date 01 22 / 04

TYPED OR PRINTED NAME

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REGISTRATION NO.
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43,972

☐ Additional inventors are being named on separately numbered sheets attached hereto**PROVISIONAL APPLICATION FOR PATENT FILING ONLY**

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SELECTIVE ESTROGEN RECEPTOR MODULATORS**Field of Invention**

The present invention is in the field of medicine, particularly in the treatment of
5 gynecological disorders. More specifically, the present invention relates to selective
estrogen receptor modulators useful to treat endometriosis and uterine leiomyoma.

Background of the Invention

10 Uterine leiomyoma/leiomyomata (uterine fibroid disease) is an old and ever
present clinical problem that goes under a variety of names, including uterine fibrosis,
uterine hypertrophy, uterine leiomyomata, myometrial hypertrophy, fibrosis uteri, and
fibrotic metritis. Essentially, uterine fibrosis is a condition where there is an inappropriate
deposition of fibroid tissue on the wall of the uterus. This condition is a cause of
dysmenorrhea and infertility in women.

15 Endometriosis is a condition of severe dysmenorrhea, which is accompanied by
severe pain, bleeding into the endometrial masses or peritoneal cavity and often leads to
infertility. The symptom's cause appears to be ectopic endometrial growths that respond
inappropriately to normal hormonal control and are located in inappropriate tissues.
Because of the inappropriate locations for endometrial growth, the tissue seems to initiate
20 local inflammatory-like responses causing macrophage infiltration and a cascade of events
leading to initiation of the painful response. Evidence suggests that a cause of uterine
fibrosis and endometriosis is an inappropriate response of fibroid tissue and/or
endometrial tissue to estrogen.

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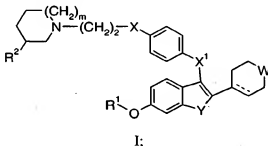
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Many publications have appeared within the last ten years disclosing novel selective estrogen receptor modulators (SERMs), *e.g.*, U.S. Patent No.'s 5,484,795, 5,484,798, 5,510,358, 5,998,401 and WO 96/09040. Many of these SERMs, generally speaking, have been found to have a beneficial estrogen agonist activity in the bone and cardiovascular systems with a concomitant beneficial estrogen antagonist activity in the breast. A small, particularly useful subset of such compounds has also been found to have an estrogen antagonist effect in the uterus. A compound with this particularly useful SERM profile holds particular promise in treating uterine leiomyoma/leiomyomata and/or endometriosis.

However, the actual use of these SERM compounds, particularly in premenopausal women, has been hampered due to said compound's stimulatory effect on the ovaries. A great need currently exists, therefore, for new SERM compounds that behave as estrogen antagonists in the uterus that do not stimulate the ovaries.

Summary of Invention

The present invention relates to a compound of formula I:



wherein:

m is 0, 1 or 2;

R¹ is H, SO₂(n-C₄-C₆ alkyl) or COR³;

R² is H or methyl provided that if m is 1 or 2, then R² must be H and that if m is 0, then R² must be methyl;

W is CHSO₂R⁴ or SO₂;

X is O or NR⁵;

X¹ is O, CH₂, or CO;

Y is S or CH=CH;

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the dashed line (---) represents an optional double bond;

R³ is C₁-C₆ alkyl, C₁-C₆ alkoxy, NR⁶R⁷, phenoxy, or phenyl optionally substituted with halo;

R⁴ is C₁-C₆ alkyl, C₁-C₆ alkoxy, NR⁸R⁹, CF₃ or CH₂CF₃;

5 R⁵ is H or C₁-C₆ alkyl

R⁶, R⁷ and R⁸ are independently H, C₁-C₆ alkyl or phenyl; and

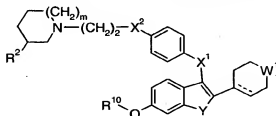
R⁹ is C₁-C₆ alkyl or phenyl; or a pharmaceutical acid addition salt thereof.

The present invention also relates to a pharmaceutical composition containing a compound of formula I, or a pharmaceutical acid addition salt thereof, and a
10 pharmaceutical carrier. In another embodiment, the pharmaceutical composition of the present invention may be adapted for use in treating endometriosis and/or uterine leiomyoma.

The present invention also relates to methods for treating endometriosis and/or uterine leiomyoma employing a compound of formula I, or a pharmaceutical acid addition
15 salt thereof.

In addition, the present invention relates to a compound of formula I, or a pharmaceutical acid addition salt thereof, for use in treating endometriosis and/or uterine leiomyoma. The present invention is further related to the use of a compound of formula I, or a pharmaceutical acid addition salt thereof, for the manufacture of a medicament for
20 treating endometriosis and/or uterine leiomyoma.

The present invention further relates to a compound of formula II:



II;

wherein:

25 m, R², R³, R⁴, X¹ and Y are as defined above for a formula I compound and W¹ is CHS(O)_nR⁴ or S(O)_n;

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n is 0, 1 or 2;

R¹⁰ is H, C₁-C₆ alkyl, benzyl, SO₂CH₃, SO₂(n-C₄-C₆ alkyl) or COR⁴;

X² is O or NR¹¹; and

R¹¹ is H, C₁-C₆ alkyl or CO₂(C₁-C₆ alkyl); provided that if n is 2, then R¹⁰ is

- 5 C₁-C₆ alkyl, SO₂CH₃ or benzyl or R¹¹ is CO₂(C₁-C₆ alkyl); or an acid addition salt thereof; useful as an intermediate to a compound of formula I.

Detailed Description

- 10 Unless specified otherwise, reference hereafter to a "compound of formula I" includes the pharmaceutical acid addition salts thereof.

- The compounds of the present invention have one or more chiral centers and may exist in a variety of stereoisomeric configurations. As a consequence of these chiral centers, the compounds of the present invention occur as racemates, mixtures of enantiomers and as individual enantiomers, as well as diastereomers and mixtures of diastereomers. All such racemates, enantiomers, and diastereomers are within the scope of the present invention.
- 15

For the purposes of the present invention, as disclosed and claimed herein, the following terms are defined below.

- The term "halo" refers to fluoro, chloro, bromo and iodo. The term "C₁-C₆ alkyl" represents a straight, branched or cyclic hydrocarbon moiety having from one to six carbon atoms, *e.g.*, methyl, ethyl, n-propyl, isopropyl, cyclopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, cyclobutyl, pentyl, cyclopentyl, hexyl, cyclohexyl and the like. Moieties such as a cyclobutylmethylenyl are also included within the scope of a C₁-C₆ alkyl group.
- 20
- The term "C₁-C₄ alkyl" refers specifically to methyl, ethyl, n-propyl, isopropyl, cyclopropyl, n-butyl, isobutyl, sec-butyl, t-butyl and cyclobutyl. The term "n- C₄-C₆ alkyl" refers specifically to n-butyl, n-pentyl and n-hexyl. A "C₁-C₆ alkoxy" group is a C₁-C₆ alkyl moiety connected through an oxy linkage.
- 25

The term "pharmaceutical" when used herein as an adjective means substantially non-deleterious.

A pharmaceutical "acid addition salt" is a salt formed by reaction of the free base form of a compound of formula I with a pharmaceutical acid, such as described in the Encyclopedia of Pharmaceutical Technology, editors James Swarbrick and James C. Boylan, Vol 13, 1996 "Preservation of Pharmaceutical Products to Salt Forms of Drugs and Absorption". Specific salt forms include, but are not limited to the: acetate, benzoate, benzenesulfonate, 4-chlorobenzenesulfonate; citrate; ethanesulfonate; fumarate; d-gluconate; d-glucuronate; glutarate; glycolate; hippurate; hydrochloride; 2-hydroxyethanesulfonate; dl-lactate; maleate; d-malate; l-malate; malonate; d-mandelate; l-mandelate; methanesulfonate; 1,5 naphthalenedisulfonate; 2-naphthalenesulfonate; phosphate; salicylate; succinate; sulfate; d-tartrate; l-tartrate; and p-toluenesulfonate.

The term "patient" as used herein refers to female humans and non-human female animals such as companion animals (dogs, cats, horses and the like).

The terms "treating" and "treat" as used herein means alleviating, ameliorating, preventing, prohibiting, restraining, slowing, stopping, or reversing the progression or severity of a pathological condition, or sequela thereof, described herein. The term "preventing" means reducing the likelihood that the recipient of a compound of formula I will incur, further incur or develop any of the pathological conditions, or sequela thereof, described herein.

The term "a patient in need thereof" is a patient either suffering from the caimed pathological condition or sequela thereof or is a patient at a recognized risk thereof as determined by medical diagnosis, *i.e.*, as determined by the attending physician.

As used herein, the term "effective amount" means an amount of a compound of formula I that is capable of treating the conditions described herein.

Preferred Compounds and Embodiments of the Invention

Certain compounds of the invention are particularly interesting and are preferred. The following listing sets out several groups of preferred compounds. It will be understood that each of the listings may be combined with other listings to create additional groups of preferred compounds.

- a) m is 1 or 2;
- b) m is 1;

- c) R^1 is H;
- d) R^1 is H or COR^3 and R^3 is C_1-C_6 alkyl, $NHCH_3$ or phenyl;
- e) R^1 is H or COR^3 and R^3 is C_1-C_4 alkyl, $NHCH_3$ or phenyl;
- f) R^4 is C_1-C_4 alkyl, NR^8R^9 or CF_3 and R^8 is H or C_1-C_4 alkyl and R^9 is C_1-C_4 alkyl;
- g) R^4 is methyl, ethyl, cyclopropyl, $NHCH_3$, $N(CH_3)_2$ or CF_3 ;
- h) R^4 is methyl or $N(CH_3)_2$;
- i) R^4 is methyl;
- j) R^4 is $N(CH_3)_2$;
- k) X is O;
- l) X is NR^5 and R^5 is H or methyl;
- m) X^1 is O or CH_2 ;
- n) X^1 is O;
- o) Y is S;
- p) Y is $CH=CH$;
- q) W is $CHSO_2R^4$;
- r) W is SO_2 ;
- s) the optional double bond is not present and W is SO_2 ;
- t) the optional double bond is not present and W is $CHSO_2R^4$;
- u) the optional double bond is present and W is $CHSO_2R^4$;
- v) the hydrochloride salt form.

The preferred patient of treatment is a female human.

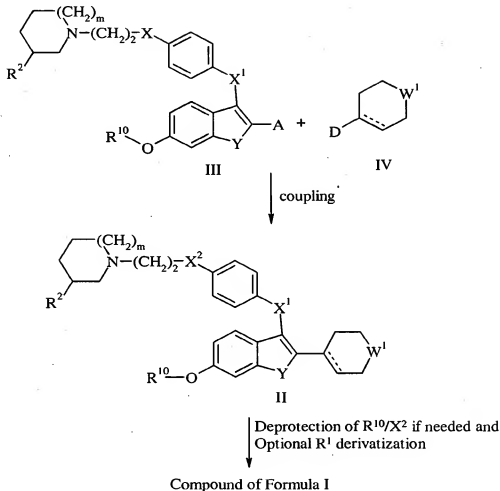
The compound of formula I is preferably formulated in a dosage unit form, i.e., in an individual delivery vehicle, for example, a tablet or capsule, prior to administration to the recipient woman.

The compound of formula I is preferably administered orally.

Synthesis

The compound of formula I may be prepared as described in the following Schemes and Examples.

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Scheme 1

In Scheme 1, a compound of formula III is reacted with a compound of formula IV under usual "Suzuki" or "Stille" reaction conditions, *i.e.*, wherein one of substituent "A" or "D" is a boronic acid/ester or alkyl stannane moiety and the other is a leaving group, *e.g.*, chloro, bromo or iodo or a sulfonate group such as trifluoromethyl sulfonate to give the compound of formula II. When R^{10} is SO_2CH_3 , C_1 - C_6 alkyl or benzyl (preferably methyl, benzyl or SO_2CH_3) said hydroxy protecting groups may be removed under

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standard conditions (see, *e.g.*, the procedures that follow or the latest edition of Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, New York, N.Y.) to provide the compound of formula I where R^1 is H. Similarly, when X^2 is NR^{11} and R^{11} is $CO_2(C_1-C_6 \text{ alkyl})$, said amino protecting group may also be removed as taught in Greene.

- 5 A formula I compound where R^1 is H may be further derivatized employing standard acylation or sulfonylation methodology to prepare a compound of formula I where R^1 is COR^3 or $SO_2(n-C_4-C_6 \text{ alkyl})$. In addition, when n is 0 or 1, the compound of formula II may be oxidized to the corresponding sulfone under standard conditions. Similarly, when the optional double bond is present in a compound of formula I or II, said double bond
10 may be reduced under standard conditions.

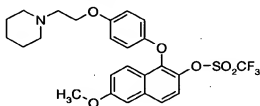
General Experimental Details

- Electrospray mass spectra may be obtained on a Finnigan LCQ Duo instrument using a mobile phase of 50% acetonitrile, 25% methanol, and 25% 2mM aqueous
15 ammonium acetate. Preparative HPLC's may be obtained on a Gilson Preparative System with Unipoint Software and dual wavelength detection at 220 and 254 nm as well as Finnigan aQa MS. A 20-mm x 250-mm ODS-AQ column with a particle size of 15 microns may be used as the stationary phase. The eluent was a binary system of bottle A (0.1% trifluoroacetic acid (TFA), 1% isopropyl alcohol (IPA) in water) and bottle B
20 (0.05% TFA, 1% IPA in acetonitrile). The standard method was a gradient of 30-95% B unless otherwise indicated. The compounds purified by this method were isolated as TFA salts.

- Preparative HPLC's may also be obtained on a Biotage ParallelFlex system with proprietary dual wavelength detection and software. A 30-mm x 150-mm or 19-mm x
25 250 mm Xterra column with a particle size of 10 microns is used as the stationary phase and 10mM $NH_4^+HCOO^-$ /10mM NH_4OH is used as mobile phase A and 100% acetonitrile is used as a mobile phase B.

Preparation 1

Trifluoromethanesulfonic acid 6-methoxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl ester



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Add 6-methoxynaphthalene-2-ol (20 g, 114.8 mmol) to dimethylformamide (DMF, 250 mL) at ambient temperature followed by *N*-bromosuccinimide (NBS, 21.5 g, 120 mmol) over a 30-minute period. After 45 minutes, dilute with water (800 mL), collect and dry the precipitate to provide 25.5 g (87%) of 1-bromo-6-methoxy-naphthalen-2-ol.

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Add 1-bromo-6-methoxy-naphthalen-2-ol (66.7 g, 264 mmol), potassium carbonate (K_2CO_3 , 40.0 g, 290 mmol) and benzyl bromide (49.6 g, 290 mmol) to DMF (800 mL). Stir the mixture at ambient temperature for 1 hour. Add water (400 mL) to precipitate the product. Collect the precipitate and wash the filter cake with heptane (3X 125 mL) then dry to provide 83.7 g of 2-benzyloxy-1-bromo-6-methoxy-naphthalene (86.2%).

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Combine toluene (200 mL), 2-benzyloxy-1-bromo-6-methoxy-naphthalene (30 g, 87.4 mmol), 4-(2-piperidin-1-yl-ethoxy)phenol (23.2 g, 105 mmol) and cesium carbonate (34.4 g, 105 mmol), heat the mixture to reflux. Remove a portion of the toluene (100 mL). Add ethyl acetate (390 mg, 4.37 mmol) and copper triflate benzene complex (2.20 g, 4.37 mmol) to the reaction mixture and stir for 5 minutes. Remove the solvent by distillation and heat the resulting residue to 174°C for 1.5 hours. Dissolve the residue in a mixture of ethyl acetate (200 mL) and aqueous hydrochloric acid (1 N, 90 mL). Separate and concentrate the organics to a residue. Column chromatograph the residue to give 12.4 g of 1-{2-[4-(2-benzyloxy-6-methoxy-naphthalen-1-yloxy)-phenoxy]-ethyl}-piperidine (30%).

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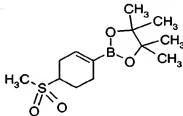
Add 1-{2-[4-(2-benzyloxy-6-methoxy-naphthalen-1-yloxy)-phenoxy]-ethyl}-piperidine (12.4 g, 25.5 mmol) to a methanol/ethyl acetate mixture (1:1, 490 mL) and heat

to form a solution. Remove the heat and add ammonium formate (4.83 g, 76.6 mmol) and $\text{Pd}(\text{OH})_2$ on Carbon (20 % ww, 1.58 g, 1.12 mmol). Reflux for 50 minutes then filter the mixture. Concentrate the filtrate to provide 9.9 g of 6-methoxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalene-2-ol (98.5%).

5 Cool dichloromethane (290 mL), triethylamine (3.08 g, 30.4 mmol) and 6-methoxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalene-2-ol (9.2 g, 23.4 g) to -50°C and add trifluoromethane sulfonic acid anhydride (7.26 g, 25.7 mmol). Stir the resulting mixture at -50°C for 2 hours then allow the mixture to warm to ambient temperature before stirring for an additional hour. Add brine (150 mL) and separate the
10 organics. Wash the organics with NaHCO_3 then dry before concentrating to a residue. Crystallize the residue with ethyl ether – hexanes to provide 11.2 g of the title compound (90.9%).

Preparation 2

(+/-)-2-(4-Methanesulfonyl-cyclohex-1-enyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane



15 Combine vinyl sulfone (5 mL, 28.9 mmol), 2-trimethylsilyloxy-butadiene (2.8 g, 31.7 mmol), and toluene (25 mL) in a 50 mL round bottom flask fitted with a reflux condenser. Heat the reaction to reflux for 48 hours. Cool to ambient temperature and concentrate *in vacuo*. Dilute with dichloromethane (50 mL) and filter through Celite and concentrate *in vacuo*. Dissolve in methanol (5 mL) and trifluoroacetic acid (2 mL) and stir at ambient temperature for 2 hours. Concentrate *in vacuo*. Purify the residue by column chromatography using a silica gel column eluting with ethyl acetate. Isolate 1.0 g (26%) of 4-methanesulfonyl-cyclohexanone after concentrating the fractions.

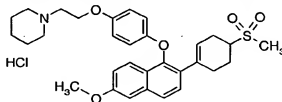
25 Combine 4-methanesulfonyl-cyclohexanone (1.0 g, 5.7 mmol), 2,6-di-*t*-butyl-4-methylpyridine (2.6 g, 12.5 mmol), and dichloromethane (10 mL) in a 25 mL round bottom flask fitted with a reflux condenser. Add triflic anhydride (1.9 mL, 11.3 mmol). Heat the reaction to reflux for 12 hours. Cool to ambient temperature and pour into ether

(150 mL). Filter and concentrate *in vacuo*. Purify the residue by column chromatography using a silica gel column eluting with a linear gradient beginning with hexanes and ending with 2:5 hexanes:ethyl acetate. Isolate 1.4 g (82%) of (+/-)-trifluoro-methanesulfonic acid 4-methanesulfonyl-cyclohex-1-enyl ester after concentrating the fractions.

- 5 Combine (+/-)-trifluoro-methanesulfonic acid 4-methanesulfonyl-cyclohex-1-enyl ester (500 mg, 1.6 mmol), bis(pinacolatodiboron) (450 mg, 1.8 mmol) and dimethylsulfoxide (5 mL). Bubble nitrogen through this solution for 15 minutes. Add potassium acetate (480 mg, 4.9 mmol) and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium dichloromethane adduct (120 mg, 0.16 mmol). Heat the mixture to 70°C for 12 hours. Cool to ambient temperature. Partition between ether (50 mL) and saturated aqueous brine (15 mL). Extract the organic component. Dry over magnesium sulfate, filter, and concentrate *in vacuo*. Purify the residue by column chromatography using a 5% triethylamine/hexanes prewashed silica gel column eluting with 5:1 ethyl acetate:hexanes. Isolate 400 mg (86%) of (+/-)-2-(4-methanesulfonyl-cyclohex-1-enyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane after concentrating the fractions.

Example 1

(+/-)-1-(2-{4-[2-(4-Methanesulfonyl-cyclohex-1-enyl)-6-methoxy-naphthalen-1-yloxy]-phenoxy}-ethyl)-piperidine Hydrochloride



- 20 Combine trifluoro-methanesulfonic acid 6-methoxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl ester (910 mg, 1.7 mmol) and (+/-)-2-(4-methanesulfonyl-cyclohex-1-enyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (990 mg, 3.5 mmol) in acetonitrile (20 mL). Bubble nitrogen through the solution for 10 minutes. Add palladium(II) acetate (39 mgs, 0.2 mmol), tricyclohexylphosphine (0.5 mL, 0.3 mmol, 20% solution in toluene), and cesium fluoride (2.4 g, 15.6 mmol). Fit the flask with a

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reflux condenser and heat to reflux for 30 minutes. Cool to ambient temperature and dilute with dichloromethane (50 mL) and saturated aqueous ammonium chloride (10 mL). Separate the organic and wash the aqueous twice with dichloromethane (10 mL).

Combine the organics and dry over magnesium sulfate. Filter and concentrate *in vacuo*.

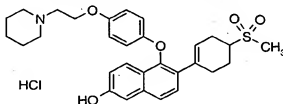
- 5 Purify the residue by column chromatography using a silica gel column eluting with a linear gradient beginning with dichloromethane and ending with 5:1 dichloromethane:methanol. Isolate 900 mg (95%) of (+/-)-1-(2-{4-[2-(4-methanesulfonyl-cyclohex-1-enyl)-6-methoxy-naphthalen-1-yloxy]-phenoxy}-ethyl)-piperidine after concentrating the fractions: mass spectrum (ion spray): $m/z = 536.2$ (M+H).

Dissolve (+/-)-1-(2-{4-[2-(4-methanesulfonyl-cyclohex-1-enyl)-6-methoxy-naphthalen-1-yloxy]-phenoxy}-ethyl)-piperidine (500 mg, 0.93 mmol) in CH_2Cl_2 (20 mL). Add hydrogen chloride (1.2 mL, 1.0 M in ether) and stir the reaction mixture for 10 minutes. Concentrate *in vacuo*. Isolate the title compound, 530 mg (100%): mass

spectrum (ion spray): $m/z = 536.2$ (M+H-HCl).

Example 2

(+/-)-6-(4-Methanesulfonyl-cyclohex-1-enyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-ol Hydrochloride



20 Dissolve (+/-)-1-(2-{4-[2-(4-Methanesulfonyl-cyclohex-1-enyl)-6-methoxy-naphthalen-1-yloxy]-phenoxy}-ethyl)-piperidine Hydrochloride (530 mg, 0.93 mmol) in CH_2Cl_2 (20 mL) and 2-methyl-1-butene (5 mL). Cool the solution to 0°C and add BBr_3 (0.3 mL, 3.3 mmol). Allow to warm to ambient temperature over 1 hour. Add methanol (10 mL) and stir 30 minutes. Add silica gel (5 g) and concentrate *in vacuo*. Purify the residue by column chromatography using a silica gel column eluting with a linear gradient beginning with dichloromethane and ending with 5:1 dichloromethane:methanol. Isolate

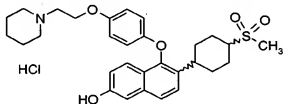
400 mg (82%) of (+/-)-6-(4-methanesulfonyl-cyclohex-1-enyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-ol after concentrating the fractions: mass spectrum (ion spray): m/z = 522.2 (M+H).

- 5 Dissolve (+/-)-6-(4-methanesulfonyl-cyclohex-1-enyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-ol (400 mg, 0.77 mmol) in CH_2Cl_2 (5 mL). Add hydrogen chloride (1 mL, 1.0 M in ether) and stir the reaction mixture for 10 minutes. Concentrate *in vacuo*. Stir the residue with ethanol (10 mL). Filter and dry the solid *in vacuo* to give 290 mg (60%) of the title compound: mass spectrum (ion spray): m/z = 522.2 (M+H-HCl).

10

Examples 3, 4 and 5

6-*cis*-and-*trans*-(4-Methanesulfonyl-cyclohexyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-ol Hydrochloride and a Mixture thereof



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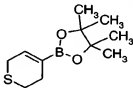
- 15 Dissolve (+/-)-1-(2-{4-[2-(4-methanesulfonyl-cyclohex-1-enyl)-6-methoxy-naphthalen-1-yloxy]-phenoxy}-ethyl)-piperidine (250 mg, 0.48 mmol) in tetrahydrofuran (25 mL) and ethanol (25 mL). Add palladium black (100 mg) and pressurize the reaction vessel with hydrogen (50 psi). Heat the reaction to 50°C for 12 hours. Cool to ambient temperature and filter through Celite, rinsing the pad with tetrahydrofuran (100 mL). Concentrate *in vacuo*. Redissolve the residue in dichloromethane (20 mL) and treat with hydrogen chloride (1 mL, 1.0 M in ether). Concentrate *in vacuo*. Redissolve the residue in dichloromethane (20 mL) and cool to 0°C. Add boron tribromide (0.15 mL, 1.6 mmol) and warm to ambient temperature for 1 hour. Add methanol (10 mL) and concentrate *in vacuo* in the presence of silica gel (5 g). Purify the residue by column chromatography using a silica gel column eluting with a linear gradient beginning with dichloromethane and ending with 5:1 dichloromethane:methanol. Combine the fractions containing product and concentrate *in vacuo*. Redissolve the residue in dichloromethane (20 mL)
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and treat with hydrogen chloride (1 mL, 1.0 M in ether). Dry the solid overnight *in vacuo* to give 160 mg (61%) of the title compounds as a 2:1 mixture of *trans:cis* isomers: mass spectrum (ion spray): $m/z = 524.2$ (M+H-HCl). (Example 3)

Separate the individual isomers (20 mg of the mixture) by chiral chromatography (Chiralpak AD column) using a 3:2 ethanol:hexanes with 0.2% dimethylethylamine
5 eluent. Individually dissolve the residues in dichloromethane (2 mL) and treat with hydrogen chloride (0.1 mL, 1.0 M in ether). Dry the solids overnight *in vacuo*. Isolate 6-*trans*-(4-methanesulfonyl-cyclohexyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-
naphthalen-2-ol hydrochloride (9 mgs, Example 4) and 6-*cis*-(4-methanesulfonyl-
10 cyclohexyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-ol hydrochloride (7 mgs, Example 5).

Preparation 3

2-(3,6-Dihydro-2H-thiopyran-4-yl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane

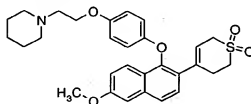


Combine diisopropylamine (2.5 mL, 18.1 mmol) and tetrahydrofuran (25 mL) and cool to 0°C. Add *n*-butyllithium (11 mL, 18.1 mmol, 1.6 M in hexanes) dropwise over 15 minutes. Cool to -78°C. Add tetrahydro-thiopyran-4-one (2 g, 17.2 mmol) dropwise over
20 20 minutes as a solution in tetrahydrofuran (20 mL). Stir at -78°C for 20 minutes. Add *N*-phenylbis(trifluoromethanesulfonylimide) (6.8 g, 18.9 mmol) from a powder addition funnel and rinse into the reaction with tetrahydrofuran (5 mL). Allow to warm to ambient temperature and stir overnight. Partition between ether (100 mL) and 1 M aqueous sodium hydroxide (25 mL). Separate organic and wash with 1 M aqueous sodium
25 bisulfate (25 mL) and finally with saturated aqueous brine. Dry the organic over sodium sulfate, decant, and concentrate *in vacuo*. Purify the residue by column chromatography using a silica gel column eluting with a linear gradient beginning with hexanes and ending with 5:1 hexanes:ethyl acetate. Isolate 3.5 g (81%) of trifluoro-methanesulfonic acid 3,6-dihydro-2H-thiopyran-4-yl ester after concentrating the fractions.

Combine trifluoro-methanesulfonic acid 3,6-dihydro-2H-thiopyran-4-yl ester (1 g, 4.0 mmol), bis(pinacolatodiboron) (1.1 g, 4.4 mmol) and dimethylsulfoxide (15 mL). Bubble nitrogen through this solution for 15 minutes. Add potassium acetate (1.2 g, 12 mmol) and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium dichloromethane adduct (290 mg, 0.40 mmol). Heat the mixture to 70°C for 12 hours. Cool to ambient temperature. Partition between ether (100 mL) and water (25 mL). Extract the organic component. Wash the organic with saturated aqueous brine (25 mL). Dry over sodium sulfate, decant, and concentrate *in vacuo*. Purify the residue by column chromatography using a 5% triethylamine/hexanes prewashed silica gel column eluting with 1:1 ether:hexanes to give 900 mg (100%) of 2-(3,6-dihydro-2H-thiopyran-4-yl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane after concentrating the fractions.

Example 6

1-(2-{4-[2-(1,1-Dioxo-1,2,3,6-tetrahydro-1λ⁶-thiopyran-4-yl)-6-methoxy-naphthalen-1-yloxy]-phenoxy}-ethyl)-piperidine



Combine trifluoromethanesulfonic acid 6-methoxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl ester (780 mg, 1.5 mmol) and 2-(3,6-dihydro-2H-thiopyran-4-yl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (700 mg, 3.0 mmol) in acetonitrile (25 mL). Bubble nitrogen through the solution for 10 minutes. Add palladium(II) acetate (34 mg, 0.15 mmol), tricyclohexylphosphine (0.36 mL, 0.23 mmol, 20% solution in toluene), and cesium fluoride (2.0 g, 13.3 mmol). Fit the flask with a reflux condenser and heat to reflux for 4 hours. Cool to ambient temperature and dilute with dichloromethane (50 mL) and saturated aqueous ammonium chloride (10 mL). Separate the organic and wash the aqueous twice with dichloromethane (10 mL). Combine the organics and dry over magnesium sulfate. Filter and concentrate *in vacuo*. Purify the residue by column chromatography using a silica gel column eluting with a linear gradient beginning with

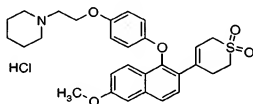
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dichloromethane and ending with 5:1 dichloromethane:methanol to give 650 mg (90%) of 1-(2-{4-[2-(3,6-dihydro-2H-thiopyran-4-yl)-6-methoxy-naphthalen-1-yloxy]-phenoxy}-ethyl)-piperidine after concentrating the fractions.

Redissolve in methanol (10 mL) and dichloromethane (20 mL). Add water (8 mL) and oxone (2.0 g, 3.4 mmol). Stir at ambient temperature for 4 hours. Dilute with dichloromethane (50 mL) and saturated aqueous sodium bicarbonate. Separate the organic, dry over magnesium sulfate, filter and concentrate *in vacuo*. Purify the residue by column chromatography using a silica gel column eluting with a linear gradient beginning with dichloromethane and ending with 5:1 dichloromethane:methanol to give 370 mg (53%) of the title compound after concentrating the fractions: mass spectrum (ion spray): $m/z = 508.1$ (M+H).

Example 7

1-(2-{4-[2-(1,1-Dioxo-1,2,3,6-tetrahydro-1 λ^6 -thiopyran-4-yl)-6-methoxy-naphthalen-1-yloxy]-phenoxy}-ethyl)-piperidine Hydrochloride

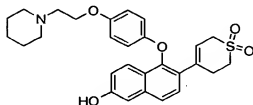


Dissolve 1-(2-{4-[2-(1,1-dioxo-1,2,3,6-tetrahydro-1 λ^6 -thiopyran-4-yl)-6-methoxy-naphthalen-1-yloxy]-phenoxy}-ethyl)-piperidine (400 mg, 0.77 mmol) in CH_2Cl_2 (5 mL). Add hydrogen chloride (1 mL, 1.0 M in ether) and stir the reaction mixture for 10 minutes. Concentrate *in vacuo* to give the title compound, 390 mg (100%); mass spectrum (ion spray): $m/z = 508.1$ (M+H-HCl).

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Example 8

6-(1,1-Dioxo-1,2,3,6-tetrahydro-1 λ^6 -thiopyran-4-yl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-ol



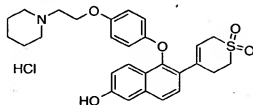
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Dissolve 1-(2-[4-[2-(1,1-dioxo-1,2,3,6-tetrahydro-1 λ^6 -thiopyran-4-yl)-6-methoxy-naphthalen-1-yloxy]-phenoxy]-ethyl)-piperidine hydrochloride (370 mg, 0.72 mmol) in CH_2Cl_2 (10 mL) and 2-methyl-1-butene (2 mL). Cool the solution to 0°C and add BBr_3 (0.24 mL, 2.5 mmol). Allow to warm to ambient temperature over 1 hour. Add methanol (10 mL) and stir 30 minutes. Add silica gel (5 g) and concentrate *in vacuo*. Purify the residue by column chromatography using a silica gel column eluting with a linear gradient beginning with dichloromethane and ending with 5:1 dichloromethane:methanol to give 290 mg (82%) of the title compound after concentrating the fractions: mass spectrum (ion spray): $m/z = 494.1$ (M+H).

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Example 9

6-(1,1-Dioxo-1,2,3,6-tetrahydro-1 λ^6 -thiopyran-4-yl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-ol Hydrochloride



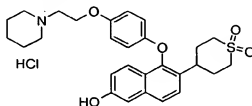
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Dissolve 6-(1,1-dioxo-1,2,3,6-tetrahydro-1 λ^6 -thiopyran-4-yl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-ol (290 mg, 0.59 mmol) in CH_2Cl_2 (5 mL). Add hydrogen chloride (1 mL, 1.0 M in ether) and stir the reaction mixture for 10 minutes. Concentrate *in vacuo*. Dissolve in methanol (5 mL) and add water (1.5 mL). Filter

through decolorizing carbon and concentrate *in vacuo* to give 180 mg of the title compound (60%): mass spectrum (ion spray): m/z = 494.1 (M+H-HCl).

Example 10

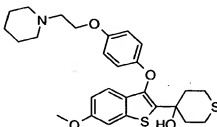
- 5 6-(1,1-Dioxo-hexahydro-1 λ^6 -thiopyran-4-yl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-ol Hydrochloride



- Dissolve 6-(1,1-dioxo-1,2,3,6-tetrahydro-1 λ^6 -thiopyran-4-yl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-ol hydrochloride (100 mg, 0.2 mmol) in tetrahydrofuran (15 mL) and methanol (10 mL). Add palladium black (50 mgs) and pressurize the reaction vessel with hydrogen (55 psi). Heat the reaction to 60°C for 12 hours. Cool to ambient temperature and filter through Celite, rinsing the pad with tetrahydrofuran (100 mL). Concentrate *in vacuo*. Redissolve the residue in dichloromethane (20 mL) and treat with hydrogen chloride (1 mL, 1.0 M in ether). Concentrate *in vacuo*. Redissolve the residue in dichloromethane (5 mL) and cool to 0°C. Add boron tribromide (75 μ L, 1.6 mmol) and warm to ambient temperature for 1 hour. Add methanol (5 mL) and concentrate *in vacuo* in the presence of silica gel (5 g). Purify the residue by column chromatography using a silica gel column eluting with a linear gradient beginning with dichloromethane and ending with 5:1 dichloromethane:methanol. Combine the fractions containing product and concentrate *in vacuo*. Redissolve the residue in dichloromethane (5 mL) and treat with hydrogen chloride (1 mL, 1.0 M in ether). Dry the solid overnight *in vacuo* to give 40 mg (38%) of 6-(1,1-dioxo-hexahydro-1 λ^6 -thiopyran-4-yl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-ol hydrochloride: mass spectrum (ion spray): m/z = 496.1 (M+H-HCl).

Preparation 4

4-[6-Methoxy-3-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-benzo[b]thiophen-2-yl]-
tetrahydro-thiopyran-4-ol



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Dissolve 1-{2-[4-(2-bromo-6-methoxy-1,1-dioxo-1H-1λ6-benzo[b]thiophen-3-yloxy)-
phenoxy]-ethyl}-piperidine (3.0 g, 6 mmol) in tetrahydrofuran (20 mL). Add methanol
(30 mL). Add 10% palladium/carbon (0.34 g). Evacuate reaction vessel. Backfill with
hydrogen. Repeat twice. Stir reaction mixture overnight. Evacuate reaction vessel.

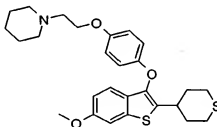
- 10 Backfill with nitrogen. Filter through Celite, rinsing with tetrahydrofuran (50 mL).
Concentrate *in vacuo*. Purify the residue by column chromatography using a silica gel
column eluting with a linear gradient beginning with dichloromethane and ending with 5 :
1 dichloromethane : methanol. Recrystallize the residue from ethanol to give 2.4 g (96%)
of 1-{2-[4-(6-methoxy-1,1-dioxo-1H-1λ6-benzo[b]thiophen-3-yloxy)-phenoxy]-ethyl}-
15 piperidine.

Dissolve 1-{2-[4-(6-methoxy-1,1-dioxo-1H-1λ6-benzo[b]thiophen-3-yloxy)-
phenoxy]-ethyl}-piperidine (14.4 g, 34.7 mmol) in dioxane (200 mL). Add
diisobutylaluminum hydride (30 mL, 168 mmol) and heat the solution to reflux for 2 h.
Cool to room temperature and then to -78 °C. Add ethyl acetate (50 mL) and warm to
20 room temperature. Pour the reaction into 10% aqueous solution of sodium potassium
tartrate. Dilute with ethyl acetate (500 mL). Stir overnight at room temperature. Transfer
to a separatory funnel. Extract the organic layer. Wash the aqueous layer with ethyl
acetate (100 mL). Combine the organics and wash with saturated aqueous brine. Dry over
sodium sulfate, decant, and concentrate *in vacuo*. Purify the residue by column
25 chromatography using a silica gel column eluting with a linear gradient beginning with
dichloromethane and ending with 7 : 1 dichloromethane : methanol to give 13.0 g (98%)
of 1-{2-[4-(6-methoxy-benzo[b]thiophen-3-yloxy)-phenoxy]-ethyl}-piperidine.

Dissolve 1-{2-[4-(6-methoxy-benzo[b]thiophen-3-yloxy)-phenoxy]-ethyl}-piperidine (1.0 g, 2.6 mmol) in tetrahydrofuran (30 mL) and cool to -78°C . Add *n*-butyllithium (1.8 mL, 2.8 mmol, 1.6 M in hexanes) and stir the reaction 15 minutes. Add tetrahydro-thiopyran-4-one (0.6 g, 5.2 mmol) as a solid and allow the reaction to stir overnight, warming to room temperature. Dilute with ethyl acetate (75 mL) and saturated aqueous ammonium chloride (25 mL). Separate the organic and wash with saturated aqueous sodium chloride. Dry over magnesium sulfate, filter, and concentrate *in vacuo* to give 1.1 g (100%) of the title compound.

Example 11

1-(2-{4-[6-Methoxy-2-(tetrahydro-thiopyran-4-yl)-benzo[b]thiophen-3-yloxy]-phenoxy}-ethyl)-piperidine



Dissolve 4-{6-methoxy-3-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-benzo[b]thiophen-2-yl}-tetrahydro-thiopyran-4-ol (1.1 g, 2.6 mmol) in dichloromethane (25 mL). Cool the solution to -78°C and add trifluoroacetic acid (6 mL). Add sodium borohydride and allow the reaction to warm to room temperature. Partition the reaction between saturated ammonium chloride (50 mL) and dichloromethane (100 mL). Separate the organic layer and dry over magnesium sulfate. Filter and concentrate *in vacuo*. Purify the residue by column chromatography using a silica gel column eluting with a linear gradient beginning with dichloromethane and ending with 5 : 1 dichloromethane : methanol to give 0.84 g (67%) of the title compound: mass spectrum (ion spray) $m/z = 484.3$ (M+H).

Example 12

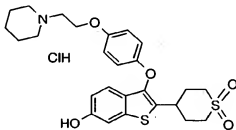
3-[4-(2-Piperidin-1-yl-ethoxy)-phenoxy]-2-(tetrahydro-thiopyran-4-yl)-benzo[b]thiophen-6-ol

- 5 Dissolve 1-(2-[4-[6-methoxy-2-(tetrahydro-thiopyran-4-yl)-benzo[b]thiophen-3-yloxy]-phenoxy]-ethyl)-piperidine (0.84 g, 1.74 mmol) in dichloromethane (10 mL). Add 1.0 M hydrogen chloride in ether (2 mL, 2 mmol) and concentrate *in vacuo*. Dissolve in dichloromethane (25 mL) and cool to 0 °C. Add boron tribromide (0.5 mL, 5.21 mmol) and allow to warm to room temperature. Stir 2 h. Cool to 0 °C and add methanol (15 mL).
- 10 Add silica gel (10 g) and concentrate *in vacuo*. Purify the residue by column chromatography using a silica gel column eluting with a linear gradient beginning with dichloromethane and ending with 5 : 1 dichloromethane : methanol to give 0.50 g (61%) of the title compound: mass spectrum (ion spray) m/z = 470.2 (M+H).

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Example 13

2-(1,1-Dioxo-hexahydro-1 λ^6 -thiopyran-4-yl)-3-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-benzo[b]thiophen-6-ol hydrochloride



- 20 Dissolve 3-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-2-(tetrahydro-thiopyran-4-yl)-benzo[b]thiophen-6-ol (0.50 g, 1.1 mmol) in dichloromethane (20 mL). Add N-methylmorpholine N-oxide (0.31 g, 2.7 mmol) and osmium tetroxide (1.1 mL, 0.11 mmol, 0.1 M solution in toluene). Stir dark brown solution 2 hours. Dilute with dichloromethane (50 mL) and 10% aqueous sodium sulfite. Stir 10 minutes and separate organic. Wash with saturated aqueous sodium bicarbonate and dry over sodium sulfate.
- 25 Decant and concentrate *in vacuo*. Purify the residue by column chromatography using a silica gel column eluting with a linear gradient beginning with dichloromethane and

ending with 5 : 1 dichloromethane : methanol. Combine the product containing fractions and concentrate *in vacuo*. Dissolve the residue in ethyl acetate and add 1.0 M hydrogen chloride in ether (1 mL). Filter the solid dry *in vacuo* at 45 °C. Isolate 0.28 g of an off-white solid (53%): mass spectrum (ion spray) $m/z = 502.2$ (M-Cl).

Formulation

Because the free base form of a compound of formula I contains a basic moiety (*i.e.*, amino), said compound may be formulated as a pharmaceutical acid addition salt, *e.g.*, as the hydrochloride salt or as a salt described in "Handbook of Pharmaceutical Salts: Properties, Selection and Use", Weinheim, New York: VHCA; Wiley-VCH, 2002.

The present pharmaceutical compositions are prepared by known procedures using well-known and readily available ingredients. In making the formulations of the present invention, the active ingredient (formula I compound) will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semisolid or liquid material which acts as a vehicle, excipient or medium for the active ingredient.

Some examples of suitable carriers, excipients, and diluents include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water syrup, methyl cellulose, methyl and propylhydroxybenzoates, talc, magnesium stearate and mineral oil. The formulations can additionally include lubricating agents, wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavoring agents.

Biological Assays

Estrogen Receptor Binding Assay: Representative compounds of the present invention are screened for binding affinity to both estrogen receptor types (ER α and ER β). This competition binding assay measures the compound's ability to displace ^3H -estradiol and generates IC₅₀ and K_i values for both receptor types.

This competition binding assay is run in a buffer containing 50mM Hepes, pH 7.5, 1.5mM EDTA, 150mM NaCl, 10% glycerol, 1mg/mL ovalbumin and 5mM DTT, using

0.025 μ Ci per well 3 H-Estradiol(NEN #NET517 at 118 Ci/mmol, 1 mCi/mL), 10 ng/well ERA α or ER β receptor (PanVera). A compound of the present invention is added at 10 different concentrations. Non-specific binding is determined in the presence of 1 μ M of 17-B Estradiol. The binding reaction (140 μ l) is incubated for 4 hours at room temperature, then 70 μ l of cold DCC buffer is added to each reaction (DCC buffer contains per 50 mL of assay buffer, 750 mg of charcoal (Sigma) and 250 mg of dextran (Pharmacia)). Plates are mixed 8 minutes on an orbital shaker at 4°C. Plates are then centrifuged at 3,000 rpm at 4°C for 10 minutes. An aliquot of 120 μ l of the mix is transferred to another 96-well, white flat bottom plate (Costar) and 175 μ l of Wallac Optiphase "Hisafe 3" scintillation fluid is added to each well. Plates are sealed and shaken vigorously on an orbital shaker. After an incubation of 2.5 hours, the plates are read in a Wallac Microbeta counter. The data is used to calculate an IC $_{50}$ and % Inhibition at 10 μ M. The K $_d$ for 3 H-Estradiol is determined by saturation binding to ER α and ER β receptors. The IC $_{50}$ values for test compounds are converted to K $_i$ using Cheng-Prusoff equation and the K $_d$ determined by saturation binding assay.

Ishikawa Cell Proliferation Assay: This assay measures cell proliferation (using an alkaline phosphatase readout) in both an agonist mode in the presence of a compound of the present invention alone, and in an antagonist mode in which the ability of a compound of the present invention to block estradiol stimulation of growth is measured.

Ishikawa human endometrial tumor cells are maintained in MEM (minimum essential medium, with Earle's salts and L-Glutamine, Gibco BRL, Gaithersburg, MD), supplemented with 10% fetal bovine serum (FBS) (V/V), (Gibco BRL). One day prior to assay, growth media is changed to assay medium, DMEM/F-12 (3:1) (Dulbecco's Modified Eagle Medium: Nutrient Mixture F-12, 3:1 Mixture, phenol red-free, Gibco BRL) supplemented with 5% dextran coated charcoal stripped fetal bovine serum (DCC-FBS) (Hyclone, Logen, UT), L-Glutamine (2mM), MEM sodium pyruvate (1 mM), HEPES (N-[2-hydroxyethyl]piperazine-N' - [2-ethanesulfonic acid] 2 mM) all from Gibco BRL). After an overnight incubation, Ishikawa cells are rinsed with Dulbecco's Phosphate Buffered Saline (1X) (D-PBS) without Ca $^{+2}$ and Mg $^{+2}$ (Gibco BRL), and trypsinized by a 3 minute incubation with 0.25% Trypsin/EDTA, phenol red-free (Gibco

BRL). Cells are resuspended in assay medium and adjusted to 250,000 cells/mL. Approximately 25,000 cells in a 100ul media are added to flat-bottom 96 wells microculture plates (Costar 3596) and incubated at 37°C in a 5% CO₂ humidified incubator for 24 hours. The next day, serial dilutions of compounds are prepared in assay
5 medium (at 6 times the final concentration in the assay). The assay is run in dual mode, agonist and antagonist modes.

For the agonist mode, plates receive 25 µl/well of assay medium followed by 25 µl/well of a diluted compound of the present invention (at 6x the final concentrations). For the antagonist mode, plates receive 25 µl/well of 6 nM E₂ (β-Estradiol, Sigma, St.
10 Louis, MO) followed by 25 µl/well of a diluted compound of the present invention (at 6x the final concentrations). After an additional 48-hour incubation at 37°C in a 5% CO₂ humidified incubator, media is aspirated from wells and 100 µl fresh assay medium is added to each microculture. Serial dilutions of compounds are prepared and added to the cells as described above. After an additional 72 hour incubation at 37°C in a 5% CO₂
15 humidified incubator, the assay is quenched by removing media and rinsing plates twice in Dulbecco's Phosphate Buffered Saline (1X) (D-PBS) (Gibco BRL). The plates are dried for 5 minutes and frozen at -70°C for at least 1 hour. The plates are then removed from the freezer and allowed to thaw at room temperature. To each well, 100 µl of 1-Step™ PNPP (Pierce Chemical Company, Rockford, IL) is added. After a 20-minute
20 incubation, plates are read on a spectrophotometer at 405nm.

The data is fitted to a linear interpolation to derive EC₅₀ (for agonist mode) or IC₅₀ (for antagonist mode) values. For the antagonist mode, a % efficacy for each compound is calculated versus E₂ (1nM) alone. For the agonist mode, a % efficacy for each compound is calculated versus the response to tamoxifen.

25 In the agonist mode, the compounds of Examples 2-5, 9, 10 12 and 13 were tested and were found to be less stimulatory than tamoxifen. For example, the compound of Example 9 had a relative % efficacy of 19%. In the antagonist mode, these same compounds inhibited greater than at least 80% of the 1nM estradiol response. For example, the compound of Example 9 had an IC₅₀ of 7.2 nM and a % efficacy of 97.9%.

MCF-7 Proliferation Assay: The MCF-7 cell line was derived from a human breast adenocarcinoma and is used as an indicator of potential antiproliferative activity in breast epithelium.

5 MCF-7 breast adenocarcinoma cells (ATCC HTB 22) are maintained in MEM (minimal essential medium, phenol red-free, Gibco BRL) supplemented with 10% fetal bovine serum (FBS) (V/V), L-glutamine (2 mM), sodium pyruvate (1 mM), HEPES ((N-[2-hydroxyethyl]piperazine-N'-[2-ethanesulfonic acid])10 mM), non-essential amino acids(0.1mM)and Penicillin Streptomycin(1X). Seven days prior to assay, MCF-7 cells
10 are switched to assay media which is the same as maintenance medium except supplemented with 10% dextran-coated charcoal-stripped fetal bovine serum (DCC-FBS) assay medium in place of 10% FBS. MCF-7 cells are removed from flasks using 10X Trypsin EDTA (phenol red free, Gibco BRL) and diluted to 1X in (Ca++/Mg++ free HBSS (phenol red-free). Cells are adjusted to 80,000 cells/mL in assay medium.
15 Approximately 8,000 cells (100 μ l) are added to each well in 96 well Cytostar T scintillation plates (Amersham) and incubated at 37°C in a 5% CO₂ humidified incubator for 24 hours to allow cell adherence and equilibration after transfer.

Serial dilutions of a compound of the present invention are prepared in assay medium at 4x the final desired concentration). A 50 μ l aliquot of test compound dilutions
20 (at 4x the final assay concentration) is transferred to duplicate wells followed by 50 μ l assay medium for the agonist mode or 50 μ l of 40pM of E2 for the antagonist mode to a final volume of 200 μ l. For each of the agonist plates, a basal level (media) and a maximum stimulated level (with 1 μ M E2) is determined. For each of the antagonist plates, a basal level (media) and an E2 (10pM) alone control is determined. After an
25 additional 48 hours at 37°C in a 5% CO₂ humidified incubator, 20 μ l of assay medium containing 0.01 μ Ci of ¹⁴C-thymidine (52 mCi/mmol, 50 μ Ci/ μ l, Amersham) is added to each well. The plates are incubated overnight in the same incubator and then counted on the Wallac Microbeta counter. The data is averaged to calculate an IC₅₀ and % inhibition @ 1 μ M for the antagonist mode. For the agonist mode, an EC₅₀ and percent of
30 maximum E2 stimulation and concentration of maximum stimulation is calculated.

3-Day Rat Uterus Antagonist Assay: This model for uterine antagonism utilizes immature (3 week old) female rats that are highly sensitive to estrogenic stimulation of the uterus given that their circulating estrogen levels are prepubertal. The uteri from immature rats are fully responsive to exogenous estrogen, yet are quiescent in the absence of exogenous estrogen. Administration of exogenous estrogen to immature rats produces a reliable elevation of uterine weight, which can be used to study uterine antagonist effects. The rats are treated with both estradiol and 4 different concentrations of a compound of the present invention for 3 days and then uterine wet weights are measured.

Nineteen to twenty-one day old (or 45-50g) female rats are orally treated with E2 (0.1 mg/kg, a maximal stimulatory estrogenic stimulus for reliably increasing uterine weight) and 10, 1.0, 0.1 and 0.01mg/kg test compound for 3 days, 6 rats per group. Test compounds are dissolved in 20% β -hydroxycyclodextrin and administered by oral gavage in a volume of 0.2 mL daily (15 min. prior to the ethynyl estradiol gavage). A vehicle control, E2 alone and E2 + raloxifene are also done as controls. The animals are fasted overnight following the final dose. On the following morning, the animals are weighed, then euthanized (by carbon dioxide asphyxiation) and the uteri rapidly collected (via a mid-line ventral incision) and weighed.

Uterine weight/body weight ratios (UWR) are calculated for each animal. The percent inhibition of the estrogen-induced response is then calculated by the following formula: $\text{percent inhibition} = 100 \times (\text{UWR}_{\text{estrogen}} - \text{UWR}_{\text{test compound}} / \text{UWR}_{\text{estrogen}} - \text{UWR}_{\text{control}})$. ED₅₀ values are derived from a semi-log regression analysis of the linear aspect of the dose response curve. Both the UWR data and the percent inhibition data were statistically analyzed by one way analysis of variance (ANOVA) with post-hoc testing by Fisher's PLSD when indicated by a $p \leq 0.05$. Statistical analyses are performed using the Statview® 4.0 software package.

The compounds of Examples 2, 3, 9 and 10 were tested in the above assay and were found to inhibit the estrogen-induced response when administered at 1.0 mg/kg. For example, the compound of Example 9 had an ED₅₀ of 0.17 mpk and a % antagonism of 72.6%.

4-Day OVX Rat Uterine Agonist Assay: In order to assure that a test compound does not have any partial uterine agonist activity, compounds are administered to mature, ovariectomized rats.

Seventy-five day old rats are ovariectomized and treatment is started 14 days later when circulating estradiol levels have reached minimal levels. After 4 days of treatment with 3 doses of a compound of the present invention, (6 rats per group) body weight, uterine wet weight and uterine eosinophil peroxidase (EPO) activity are measured. Cholesterol levels are also measured to compare relative ability to lower cholesterol with other SERMs. If there is any question of uterine stimulation, histological examination will determine epithelial cell height.

10-Day Rat Hormone (Ovarian Stimulation) Screen: An initial, first screen for ovarian toxicity is conducted using a 10-day rat hormone study to measure estradiol and luteinizing hormone levels after compound administration. This screen is conducted by administering compound by oral gavage for 10 days to mature (9-10 week old) F344 female rats. Trunk blood is collected by rapid decapitation for evaluation of LH and estradiol levels approximately 2 hours after the 10th dose. Serum, obtained by centrifugation, is removed and stored frozen below -60°C until assayed. Serum levels of LH and estradiol are measured using radioimmunoassay (RIA) methods.

Rat LH primary antibody and reference preparations (rat LH:RP-3) were obtained from Dr. A. F. Parlow, Director, Pituitary Hormones and Antisera Center, Harbor-UCLA Medical Center, Torrance, CA. The LH assay upper limits of detection were 30 ng/mL and the lower limits of detection were 0.1 ng/mL for the 100 µl samples.

E2 Clinical Assays. DiaSorin s.r.l., Saluggia (Vercelli), Italy. The upper limit of detection was 1000 pg/mL and the lower limit of detection was 5 pg/mL. The compound of Example 2 was tested in the above assay and did not significantly elevate circulating estradiol or LH levels.

35-Day Ovary-Intact Rat Bone Assay: While previous SERMs, including raloxifene have shown efficacy in preventing bone loss in OVX rats, the possibility of interference with estrogen-regulated turnover in ovary-intact rats needs to be addressed.

This assay is done in mature rats with concentrations based on the demonstrated efficacy in the 3-day assay. Generally, at least three concentrations are chosen based on multiples of the ED50 generated therein. These multiples are generally 1x, 10x and 30x the ED50. A compound of the present invention is administered to an OVX rat for 35 days and is compared to control, ovariectomized, and/or GnRH-administered rats. Femurs, tibiae, uteri, ovaries and serum are taken for further analyses. DEXA (Dual Energy X-ray Absorptivity), CT (Computed Tomography) and histologic analysis are done on the long bones to assess any changes. CT scans of the distal femur are done to calculate BMD (bone mineral density), cross sectional area and BMC (bone mineral content). Bone strength measurements (load to failure) may also be done to determine consequences of any bone mass or material changes. Uterine and ovarian histology are examined to confirm long term dosing effects of uterine efficacy and potential ovarian stimulation. The serum is analyzed for LH and E2 levels as a possible indicator of ovarian effects.

Utilities

The diseases, disorders or conditions for which a compound of formula I is useful in treating include, but are not limited to, (1) uterine cancer; (2) endometriosis; (3) uterine leiomyoma/leiomyomata; (4) post-menopausal osteoporosis, *i.e.*, osteoporosis caused by the loss of bone that results from a lack of endogenous estrogen such as occurs in a woman following cessation of menstruation due to natural, surgical, or other processes; and (5) estrogen receptor positive (ER+) breast cancer, particularly the prevention thereof. Treatment of uterine leiomyoma/leiomyomata as described herein, also contemplates the reduction of the occurrence or severity of the associated symptoms such as pain, urinary frequency, and uterine bleeding.

Dose

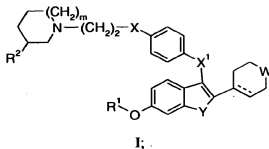
The specific dose administered is determined by the particular circumstances surrounding each situation. These circumstances include, the route of administration, the prior medical history of the recipient, the pathological condition or symptom being treated, the severity of the condition/symptom being treated, and the age of the recipient.

The recipient patient's physician should determine the therapeutic dose administered in light of the relevant circumstances.

5 Generally, an effective minimum daily dose of a compound of formula I, will exceed about 5 mg. Typically, an effective maximum daily dose will not exceed about 350 mg. The exact dose may be determined, in accordance with the standard practice in the medical arts of "dose titrating" the recipient; that is, initially administering a low dose of the compound, and gradually increasing the dose until the desired therapeutic effect is observed.

WE CLAIM:

1. A compound of formula I:



5 wherein:

m is 0, 1 or 2;

R¹ is H, SO₂(n-C₄-C₆ alkyl) or COR³;

R² is H or methyl provided that if m is 1 or 2, then R² must be H and that if m is 0, then R² must be methyl;

10 W is CHSO₂R⁴ or SO₂;

X is O or NR⁵;

X¹ is O, CH₂, or CO;

Y is S or CH=CH;

the dashed line (---) represents an optional double bond;

15 R³ is C₁-C₆ alkyl, C₁-C₆ alkoxy, NR⁶R⁷, phenoxy, or phenyl optionally substituted with halo;

R⁴ is C₁-C₆ alkyl, C₁-C₆ alkoxy, NR⁸R⁹, CF₃ or CH₂CF₃;

R⁵ is H or C₁-C₆ alkyl

R⁶, R⁷ and R⁸ are independently H, C₁-C₆ alkyl or phenyl; and

20 R⁹ is C₁-C₆ alkyl or phenyl; or a pharmaceutical acid addition salt thereof.

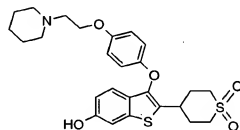
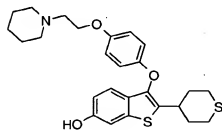
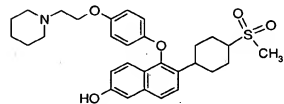
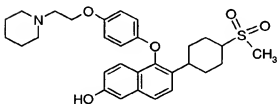
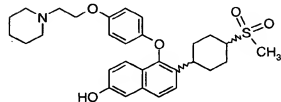
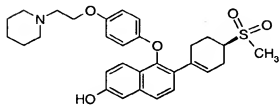
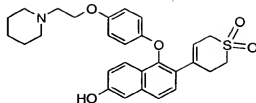
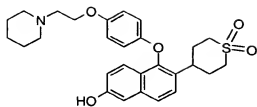
2. The compound of claim 1 wherein X and X¹ are O and m is 1 or 2.

3. The compound of claim 1 or claim 2 wherein R¹ is H or COR³ and R³ is C₁-C₄ alkyl, NHCH₃ or phenyl.

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4. The compound of any one of claims 1-3 wherein R^1 is H and m is 1.
5. The compound of any one of claims 1-4 wherein Y is $CH=CH$.
- 5 6. The compound of any one of claims 1-5 wherein W is $CHSO_2R^4$.
7. The compound of any one of claims 1-6 wherein R^4 is C_1 - C_4 alkyl, CF_3 or NR^8R^9 and R^8 is H or C_1 - C_4 alkyl and R^9 is C_1 - C_4 alkyl.
- 10 8. The compound of any one of claims 1-7 wherein R^4 is methyl, ethyl, cyclopropyl, CF_3 , $NHCH_3$ or $N(CH_3)_2$.
9. The compound of any one of claims 1-5 wherein W is SO_2 and the optional double bond is not present.
- 15 10. A compound selected from the group consisting of:

-32-



or a pharmaceutical acid addition salt thereof.

11. The compound of any one of claims 1-10 which is the hydrochloride salt.

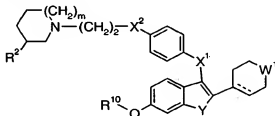
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12. A method of treating endometriosis comprising administering to a patient in need thereof an effective amount of a compound of any one of claims 1-11.

13. A method of treating uterine leiomyoma comprising administering to a patient in need thereof an effective amount of a compound of any one of claims 1-11.

- 5 14. A compound of any one of claims 1-11 for use in treating endometriosis and/or uterine leiomyoma.

15. A compound of formula II:



II;

wherein:

m is 0, 1 or 2;

R² is H or methyl provided that if m is 1 or 2, then R² must be H and that if m is 0, then R² must be methyl;

- 15 R¹⁰ is H, C₁-C₆ alkyl, benzyl, SO₂CH₃, SO₂(n-C₄-C₆ alkyl) or COR⁴;

W¹ is CHS(O)ₙR⁴ or S(O)ₙ;

X¹ is O, CH₂, or CO;

X² is O or NR¹¹;

Y is S or CH=CH;

- 20 the dashed line (---) represents an optional double bond;

n is 0, 1 or 2;

R³ is OH, C₁-C₆ alkyl, C₁-C₆ alkoxy, NR⁶R⁷, phenoxy, or phenyl optionally substituted with halo;

R⁴ is C₁-C₆ alkyl, C₁-C₆ alkoxy, NR⁸R⁹, CF₃ or CH₂CF₃;

- 25 R⁶, R⁷ and R⁸ are independently H, C₁-C₆ alkyl or phenyl;

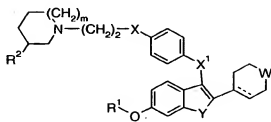
R⁹ is C₁-C₆ alkyl or phenyl; and

R¹¹ is H, C₁-C₆ alkyl or CO₂(C₁-C₆ alkyl); provided that if n is 2, then R¹⁰ is C₁-C₆ alkyl, SO₂CH₃ or benzyl or R¹¹ is CO₂(C₁-C₆ alkyl); or an acid addition salt thereof.

- 5 14. The compound of claim 13 wherein X² and Y are O and m is 1 or 2.
15. The compound of claims 13 or claim 14 wherein R¹⁰ is SO₂CH₃, benzyl or methyl.
- 10 16. The compound of any one of claims 13-15 wherein m is 1.
17. The compound of any one of claims 13-16 wherein W¹ is CHSO_nR⁴.
18. The compound of any one of claims 13-17 wherein R⁴ is C₁-C₄ alkyl, CF₃ or NR⁸R⁹ and R⁸ is H or C₁-C₄ alkyl and R⁹ is C₁-C₄ alkyl.
- 15 19. The compound of any one of claims 13-18 wherein R⁴ is methyl, ethyl, cyclopropyl, CF₃, NHCH₃ or N(CH₃)₂.
- 20 20. The compound of any one of claims 1-5 wherein W is SO₂ and the optional double bond is not present.

ABSTRACT

The present invention relates to a selective estrogen receptor modulator of formula I:



I;

or a pharmaceutical acid addition salt thereof; useful, *e.g.*, for treating endometriosis and uterine leiomyoma.